Current Diagnosis and Management of Suspected Reflux Symptoms Refractory to Proton Pump Inhibitor Therapy

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Abstract: Suspected reflux symptoms that are refractory to proton pump inhibitors (PPIs) are rapidly becoming the most common presentation of gastroesophageal reflux disease (GERD) in patients seen in gastroenterology clinics. These patients are a heterogeneous group, differing in symptom frequency and severity, PPI dosing regimens, and responses to therapy (from partial to absent). Before testing, the physician needs to question the patient carefully about PPI compliance and the timing of drug intake in relation to meals. Switching PPIs or doubling the dose is the next step, but only 20% to 25% of the group refractory to PPIs will respond. The first diagnostic test should be upper gastrointestinal endoscopy. In more than 90% of cases, the results will be normal, but persistent esophagitis may suggest pill esophagitis, eosinophilic esophagitis, or rarer diseases, such as lichen planus, Zollinger-Ellison syndrome, or genotype variants of PPI metabolism. If the endoscopy results are normal, esophageal manometry and especially reflux testing should follow. Whether patients should be tested on or off PPI therapy is controversial. Most physicians prefer to test patients off PPIs to identify whether abnormal acid reflux is even present; if it is not, PPIs can be stopped and other diagnoses sought. Testing patients on PPI therapy allows nonacid reflux to be identified, but more than 50% of patients have a normal test result, leaving the clinician with a conundrum—whether to stop PPIs or continue them because the GERD is being treated adequately. Alternative diagnoses in patients with refractory GERD and normal reflux testing include achalasia, eosinophilic esophagitis, gastroparesis, rumination, and aerophagia. However, more than 50% will be given the diagnosis of functional heartburn, a visceral hypersensitivity syndrome. Treating patients with PPI-refractory GERD–like symptoms can be difficult and frustrating. Any of the following may help: a histamine-2 receptor antagonist at night, baclofen to decrease transient lower esophageal sphincter relaxations, pain modulators, acupuncture, or hypnotherapy. At this time, antireflux surgery should be limited to patients with abnormal acid reflux defined by pH testing and a good correlation of symptoms with acid reflux.

Acid suppression with proton pump inhibitors (PPIs) is the mainstay of therapy for gastroesophageal reflux disease (GERD). Although success rates for healing esophagitis approach 80% to 90%, a large percentage of patients (10%-40%) fail to respond symptomatically, either partially or completely, to standard doses of PPIs.[1,2] These patients are said to have refractory GERD, which is one of the most common presentations of the GERD syndrome in general gastroenterology practices.[2] The patients are a heterogeneous group, differing in symptom frequency and severity, PPI dosing regimens, and responses to therapy (from partial to absent). Although studies often define a poor response to PPIs as less than a 50% reduction in the chief complaint over 8 to 12 weeks of therapy, the distinction in clinical practice is difficult. The symptoms often are not classic for reflux, tools for measuring the disease are imperfect, and each patient's perception of the remaining symptoms is subjective and depends on his or her expectations of the therapy.[3] For example, a large study in a family practice setting found that only 49% of patients with GERD had either heartburn or acid regurgitation as their most troublesome symptom, and symptom response to esomeprazole was neither sensitive nor specific for the diagnosis of GERD.[4]

The PPI regimen used to define refractory GERD is controversial. Some experts suggest that the lack of a symptomatic response to once-daily PPI dosing is sufficient to consider a patient's response to PPI therapy a failure. This definition is relevant to drug companies and third-party payors because the US Food and Drug Administration's approval for PPI dosing does not extend to twice-daily therapy.[2] However, physicians in clinical practice usually double the PPI dose, hoping for symptom resolution. Nonetheless, the majority of patients (75%) continue to experience reflux symptoms despite increased doses of PPIs.[2] These patients are a major factor in the 50% increase in twice-daily PPI use being reported in the United States and Canada, now exceeding 20% in the province of Manitoba.[5]

Refractory GERD is a patient-driven phenomenon.[1] The vast majority of patients have normal findings on endoscopy, and true GERD-related complications are rare. However, these persistent symptoms have a significant impact on quality of life. A recent systematic review of 9 studies found that refractory symptoms in patients on PPIs are associated with reductions in both physical and mental health-related quality of life.[6] Because not all patients failing to respond to PPIs have GERD, the most important goal of the diagnostic evaluation is to differentiate those with persistent reflux as the cause of their ongoing symptoms from those with non-GERD causes, both organic and functional.

Evaluation of Symptoms and Proton Pump Inhibitor Compliance

Clarification of the characteristics of the persistent symptoms and the factors that aggravate them is crucial. Heartburn is characterized by pain or discomfort of a burning quality beginning in the epigastrium and often radiating into the chest. Aggravating factors are usually foods, exercise, and the reclining position. In clinical practice, many patients with refractory heartburn experience an atypical burning sensation beginning in the upper chest or throat that is often unrelated to meals and associated with dyspepsia, belching, bloating, and throat symptoms.[4] Regurgitation is an important factor in some patients with refractory symptoms. In clinical trials, PPIs have been less effective for the relief of regurgitation than of heartburn.[7] As a result, a patient's heartburn may be relieved by PPIs, but persistent regurgitation becomes the driving complaint. The patient should be carefully assessed for the presence of associated functional disorders because of their negative impact on the treatment of reflux symptoms.[3,8] In fact, a recent study found that 3 clinical features—a body mass index below 25 kg/m^2, normal endoscopy results, and/or associated irritable bowel syndrome or functional dyspepsia—were superior to 24-hour pH-impedance parameters with the patient off antacids as predictors of a poor response to PPI therapy.[9]

As part of the clinical evaluation, physicians should carefully check the patient's compliance and ensure that PPI dosing is appropriate before ordering additional and expensive testing. Compliance with once-daily PPIs in patients who have GERD has been reported to be lower in those with refractory symptoms (46%-55%) than in those experiencing adequate relief (84%).[10] The efficacy of PPIs is generally maximized when they are taken before a meal.[11] A survey of 491 physicians in the United States found that nearly 70% of primary care physicians and 20% of gastroenterologists advised patients to take their PPI dose at bedtime or did not believe that the timing of dosing in relation to meals was important.[12]

Once compliance and appropriate dosing have been confirmed, a single trial of a different PPI can be considered. The efficacy of this approach was supported in a multicenter study of patients who had persistent heartburn while taking 30 mg of lansoprazole before breakfast. A switch to a single morning dose of 40 g of esomeprazole was as helpful as 30 mg of lansoprazole twice daily for relieving heartburn symptoms over 8 weeks.[13] Another randomized multicenter trial showed that either increasing PPI dosing to twice daily or switching to another PPI resulted in symptomatic relief in 20% of patients, without a clear advantage for either strategy.[14]

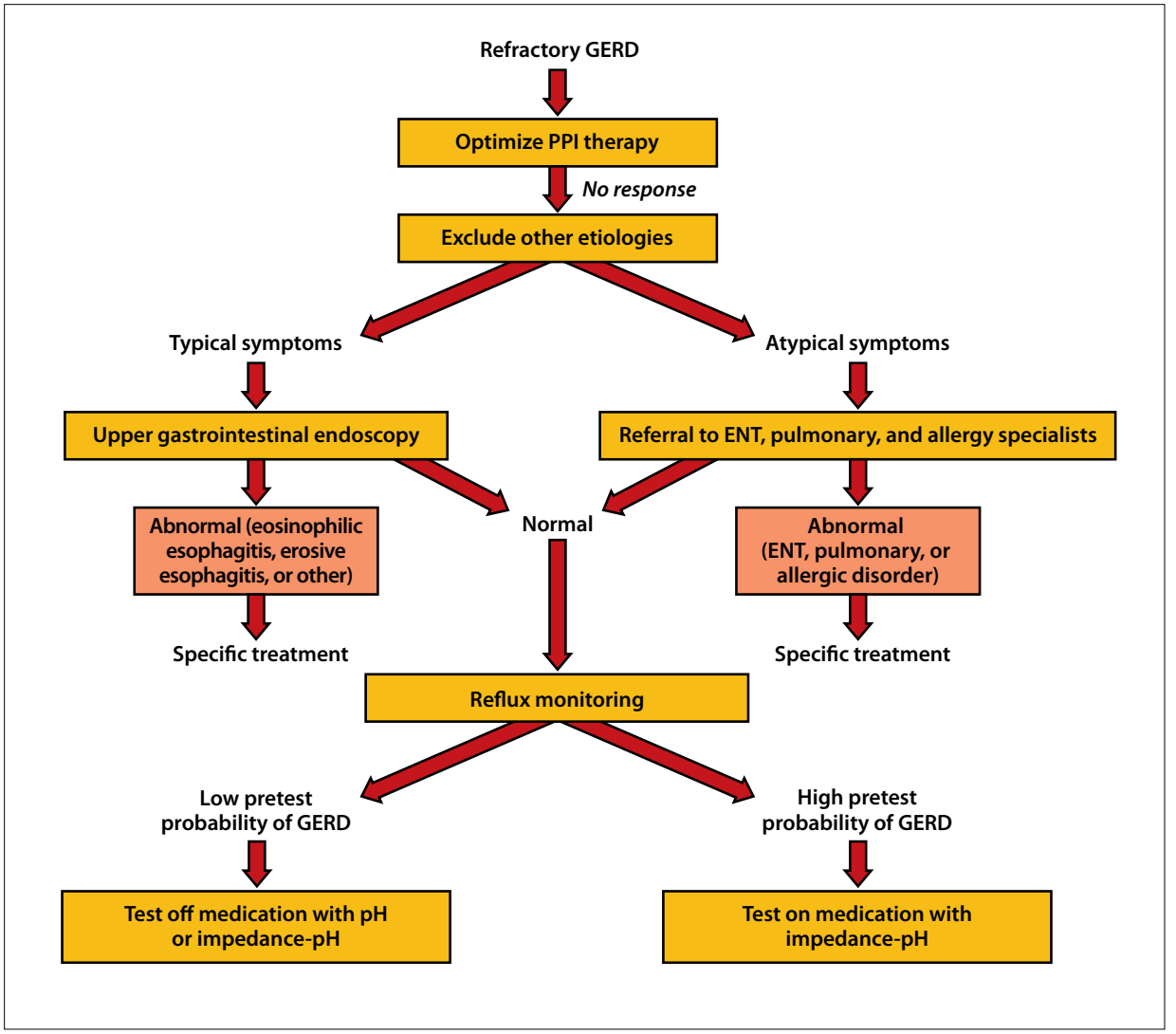

Figure. An algorithm for the evaluation of refractory GERD as suggested by the recent guidelines from the ACG.

ACG, American College of Gastroenterology; ENT, ear, nose, and throat; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

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Further Investigation of Reflux Symptoms Refractory to Proton Pump Inhibitors

Upper Gastrointestinal Endoscopy

Patients with persistent symptoms despite the optimization of PPI therapy require further work-up. A suggested algorithm was recently published by the American College of Gastroenterology (Figure).[15] It recommends that patients with typical esophageal symptoms undergo upper gastrointestinal endoscopy primarily to exclude nonreflux esophageal disorders. Those with primarily extraesophageal symptoms persisting despite twice-daily PPIs should be referred to other specialists for thorough pulmonary, otolaryngology, and allergy evaluations. However, in the gastroenterology world, all of these patients first undergo upper gastrointestinal endoscopy, and, at the present time, the procedure is nearly always performed while the patients are on PPIs.

In my experience, more than 90% of patients with refractory symptoms while on twice-daily PPI therapy have generally normal endoscopy findings. This observation was recently confirmed in a Veterans Affairs study of 100 patients, each of whom had reflux symptoms while off PPIs or were PPI failures. Endoscopy findings were completely normal in 54% of the PPI failures, compared with 41% of the patients off PPIs. In the refractory group, the most common abnormal finding was a hiatal hernia,

Table 1. Differential Diagnosis for Patients With Refractory Gastroesophageal Reflux Disease and Esophagitis

- Eosinophilic esophagitis
- Pill esophagitis
- Skin diseases with esophagitis, especially lichen planus
- Acid hypersecretory state: Zollinger-Ellison syndrome
- Genotypic differences in cytochrome P450 2C19 metabolism

but 7% had esophagitis (all Los Angeles [LA] grade A or B), 4% had Barrett esophagus, 1% had eosinophilic esophagitis, and 1% had ulcer disease. There were no upper gastrointestinal cancers.[16]

Several diagnoses should be considered in patients with refractory GERD and esophagitis (Table 1). In my experience, the most common are eosinophilic esophagitis and pill-induced esophagitis. The prevalence of eosinophilic esophagitis in patients with refractory GERD is poorly studied but likely approximately 5%[17]; however, the prevalence is much higher if dysphagia is a major complaint. Even patients with classic LA esophagitis and Schatzki rings can have eosinophilic esophagitis[18]; therefore, at least 6 biopsy specimens should be obtained from the distal and proximal esophagus. Pill-induced esophagitis should be suspected in young and elderly patients with atypical esophagitis or ulcers in the proximal or distal esophagus, but not adjacent to the squamocolumnar junction. Usually, odynophagia is a major complaint, but it may be interpreted as heartburn by the patient.[19]

Other, less common diseases are esophageal presentations of autoimmune skin diseases, acid hypersecretory states, and genotypic differences. Patients with autoimmune skin diseases are primarily middle-aged to elderly women who usually have associated dysphagia resulting from proximal strictures and who may have lesions on their skin, oral mucosa, and anogenital region.[20] The most common diagnosis is lichen planus,[21] but epidermolysis bullosa, pemphigus vulgaris, and cicatricial pemphigoid have also been reported. Endoscopy reveals diffuse erythema, blistered mucosa that is easily peeled away from the submucosa, whitish nodules, and proximal strictures.[22] Acid hypersecretory states, such as Zollinger-Ellison syndrome, may be associated with esophagitis and difficult-to-manage strictures in 30% to 45% of patients.[22] Associated symptoms include gastric and duodenal ulcers and diarrhea. The esophagitis may be difficult to manage, and intravenous PPIs are sometimes required to reduce acid production to less than 1 mEq/h.[22] Genotypic differences in cytochrome P450 2C19 enzymes, especially in the Asian population, are associated with the rapid metabolism of PPIs in 12% to 20% of these patients. This may result in persistent esophagitis, usually at once-daily, rather than twice-daily, PPI dosing.[23]

Refractory Gastroesophageal Reflux Disease With Normal Endoscopy: Role of Esophageal Function Tests

If the results of endoscopy are negative, the next step is to perform esophageal function tests, especially reflux monitoring, to quantify the presence and type of abnormal reflux and its relationship to the patient's symptoms.

Esophageal Manometry When transnasal reflux catheters are used, esophageal manometry must be performed to define the proximal border of the lower esophageal sphincter (LES) for proper placement of the pH catheter. In the United States, transnasal catheters are increasingly being replaced by wireless pH capsules, which are positioned endoscopically and do not require manometry for placement.[24] Nevertheless, achalasia and severe esophageal motor disorders must be excluded in patients with refractory symptoms because heartburn is a common symptom in up to 35% of patients with achalasia.[25]

Ambulatory Reflux Monitoring Refractory reflux symptoms are one of the most common indications for reflux testing.[2] Any of the available systems (pH alone, wireless pH capsule, or impedance-pH) is sufficiently accurate to test patients off PPI therapy to confirm or exclude the presence of abnormal acid reflux and define its relationship to symptoms. Impedance-pH testing is the only technology sufficiently accurate to measure weak and nonacid reflux in patients on PPI therapy for assessment of adequate acid control but ongoing symptomatic nonacid reflux.[26]

Clinical Questions

My approach is to address the 4 clinical questions below, tailoring my testing to the patient's PPI status to outline further treatment.

Is the proton pump inhibitor dose insufficient to control acid reflux? As previously discussed, this is rarely the case with double-dose PPIs. A retrospective study from the Cleveland Clinic found that only 7% of 175 patients with typical GERD symptoms still had abnormal acid reflux values while on twice-daily PPIs, as did none of 145 patients with extraesophageal symptoms while on twice-daily dosing.[27] Other studies suggest that up to 15% of patients may still have abnormal acid reflux.[2] Therefore, the results of traditional pH testing are most likely to be normal in patients on twice-daily PPIs, which would not exclude ongoing weak or nonacid reflux. On the other hand, studying patients with refractory symptoms while off PPI therapy for at least 1 week has the important advantage of defining whether the patients have abnormal acid reflux at all. This is critical if antireflux surgery is being planned because the best predictor of surgical success is an abnormal result of a 24- to 48-hour pH test.[28]

Table 2. Alternative Diagnoses in Patients With Refractory Reflux Symptoms and Normal Endoscopic Findings

- Achalasia
- Gastroparesis
- Eosinophilic esophagitis
- Rumination
- Aerophagia
- Functional heartburn
  - Acid-sensitive esophagus
  - Functional heartburn with no symptom relationship

In fact, most US surgeons will not operate on a patient who has refractory GERD without this documentation.[29]

Does the patient have uncontrolled weak or nonacid reflux on twice-daily proton pump inhibitors? This can be accurately measured only with impedance-pH testing because PPIs do not change the number of reflux episodes, but rather shift the pH of the refluxate from an acidic (pH <4) to a less acidic (pH 4-6) value.[30] Antimony pH electrodes cannot accurately measure weak acid, and impedance is required to identify these episodes of retrograde reflux.[26] In both of 2 large studies from the United States[31] and Europe[32] examining patients on PPI therapy (usually twice daily), nonacid reflux accounted for 37% of the abnormal study results, although the number of episodes of weak or nonacid reflux was usually not increased in these studies (ie, >73 episodes per 24 hours). Rather, the abnormal association was usually defined by a positive symptom relationship—either the symptom index (SI) in the United States or the symptom association probability (SAP) in Europe. However, these symptom analyses have been validated only for acid reflux and the symptoms of heartburn, regurgitation, and chest pain[33,34]; the analyses have not been adequately studied for extraesophageal symptoms and weak or nonacid reflux.[2] Therapies based on these nonvalidated measurements are not predictable, which helps to explain the lack of high-quality studies addressing the treatment of nonacid reflux. Most commonly, impedance-pH testing found that 50% to 60% of patients did not have reflux to account for their symptoms.[31,32] Although this finding is encouraging for the gastroenterologist, most patients will then ask what they should do with their PPIs. This is a difficult question because testing while patients are on PPIs does not allow the gastroenterologist to distinguish those with acid reflux disease and adequate control on their current PPI dose from the many patients who do not have acid reflux, in whom another diagnosis needs to be considered and the PPIs discontinued.

What is the cause of the refractory symptoms? This question is best answered if we know the true probability of the patient having acid reflux disease. Patients with typical heartburn and regurgitation partially responding to PPIs and those with endoscopic findings strongly suggestive of acid reflux disease (persistent esophagitis, Barrett esophagus, and large [>3 cm] hiatal hernia) have a high probability of having GERD and are best evaluated to address this question with impedance-pH testing while on PPI therapy. On the other hand, the vast majority of patients with refractory symptoms have atypical heartburn complaints, extraesophageal symptoms, and normal endoscopic findings, with little to no response to a multitude of different PPIs. Therefore, these patients have a low probability of having GERD and can be studied with any of the 3 pH tests while off PPIs for at least 1 week. Only 2 studies have compared the yield of reflux monitoring while the same patients with refractory GERD were off and on PPI therapy. Hemmink and colleagues[35] concluded that patients should be tested while off PPIs because this approach gave a higher yield of abnormal acid reflux exposure (12 subjects off therapy vs 10 subjects on therapy) and a positive SAP correlation (15 vs 11 subjects). In contrast, Pritchett and colleagues[36] found that reflux monitoring with patients on therapy might be the best approach.

Does the patient have abnormal acid reflux at all? I believe that this is the most important question to answer in my practice, as most of my patients (70%) have a low probability of having GERD. If third-party payors allow, I prefer to perform 48-hour and sometimes 92-hour wireless pH capsule studies to increase the likelihood of detecting abnormal acid reflux values and a correlation of symptoms with episodes of acid reflux.[37] In the experience of many large esophageal centers, the majority of these patients have no acid reflux and a poor correlation between symptoms and acid reflux. In this setting, other gastrointestinal diagnoses need to be considered (Table 2). Patients with primarily extraesophageal complaints can be referred back to otolaryngology, lung, or cardiac specialists with great confidence that GERD is not causing their symptoms and that other etiologies must be considered. Lastly, and perhaps most importantly, these patients can be encouraged to stop their PPIs and use other medications to relieve their symptoms. However, a recent retrospective study suggests that this may be more easily said than done. After a negative evaluation for refractory GERD that included normal endoscopic findings and negative results of reflux testing, 42% of 90 patients on chart review 2 years later reported continued use of PPIs despite the negative test results.[38] This study emphasizes the importance of a face-to-face conversation to educate patients about the need to stop PPIs once GERD has been ruled out. On the other hand, if patients are found to have abnormal acid reflux parameters with a strong relationship to symptoms, then these patients have

GERD, the timing of PPI medication can be adjusted, and antireflux surgery becomes a viable option.

Alternative Diagnoses in Patients With Refractory Reflux Symptoms

Table 2 outlines the important diseases that I attempt to identify after GERD has been ruled out. Achalasia is often misdiagnosed if heartburn is a predominant complaint and the esophagus is not dilated.[39] The dysphagia of these patients does not decrease with esophageal dilation, as would be expected with a peptic stricture. Esophageal manometry and high-quality barium studies will confirm the diagnosis of achalasia. Mild to moderate gastroparesis is likely the most common alternative organic disease that I find in patients with PPI-refractory symptoms. Helpful clues include the associated symptoms of pain, belching and bloating after meals, more regurgitation than heartburn, and a normal LES pressure on esophageal manometry. Most of these patients are women with idiopathic gastroparesis, confirmed by a 4-hour gastric emptying study. Eosinophilic esophagitis must be considered because heartburn can be a dominant symptom, and approximately 10% of patients will have normal endoscopic results but positive findings on esophageal biopsy.[40] Other, less common syndromes include rumination and aerophagia, which respond well to behavioral modification. Rumination should be suspected primarily in women with effortless regurgitation within the first 2 hours after a meal.[41] Their "reflux" material is usually not acidic. A recent study that used impedance-pH monitoring found that 26 patients with PPI-refractory symptoms swallowed more air during meals and had more episodes of reflux containing gas than 18 patients with PPI-responsive symptoms.[42]

After testing, up to 58% of patients will have a final diagnosis of "functional heartburn."[2] This comes in 2 forms: acid-hypersensitive esophagus and functional heartburn. Patients with the former condition have a positive association of symptoms with acid reflux, but the esophageal acid reflux parameters are normal.[43] These patients usually have a normal esophagus on endoscopic examination, frequently have dyspeptic symptoms, and are less responsive to PPIs and fundoplication than those with abnormal acid exposure, although prospective data are lacking.[2] Functional heartburn is defined by the Rome III criteria as heartburn refractory to PPIs in patients with normal endoscopic findings, normal esophageal acid reflux exposure, and a negative association of symptoms and reflux.[44] The current diagnosis is based on acid reflux monitoring only, but the addition of impedance to pH testing may increase the diagnostic yield from 29% with pH testing alone to 39%.[44] In overall studies performed with 24-hour pH-impedance testing, 21% to 40% of patients with PPI-refractory reflux symptoms are reported as having functional heartburn.[2,44,45]

Treatment of Proton Pump Inhibitor Nonresponders

As discussed, the key to successful treatment is a better understanding of the physiology causing the symptoms. In this context, one might even argue that patients who fail to obtain symptom relief after a single-dose PPI should undergo endoscopy and reflux testing before progressing to expensive and potentially dangerous double-dose PPI treatment. However, this is not realistic in a busy gastroenterology clinic, and doubling the PPI dose will always be the first next step. However, we know that only approximately 20% to 25% of this refractory group will respond.[14] What else do we have to offer these patients? The options are not great, which underscores the need to test early and then attempt to resolve the symptom issues.

Acid Suppression

In practice, patients are frequently switched to another PPI, although there are no strong scientific data to support this approach. To date, 2 studies, one controlled[46] and the other randomized,[47] support switching from a first-generation PPI to esomeprazole. This may even be cost-effective.[47] Doubling the dose of the same PPI is usually done first, but the 2 available studies[13,14] show only a 20% to 30% success rate, with 25% of subjects still experiencing refractory symptoms.

If acid is the driving factor behind persistent symptoms, logic suggests that a faster onset of action or a greater degree of acid inhibition should help. However, the results of studies with dexlansoprazole (Dexilant, Takeda) or potassium-competitive acid blockers have been disappointing. Dexlansoprazole, with its 2-stage releasing process, failed to produce any clinically significant improvement in either healing rates or esophagitis and symptom control.[48] Despite a more rapid onset of action and nearly complete acid inhibition, AZD0865 (revaprazan), a potassium-competitive acid blocker, failed to achieve any significant improvement in esophagitis healing rates or symptom relief compared with esomeprazole in 2 large clinical trials.[49,50] The development of this class of compounds has been discontinued.

Nocturnal breakthrough of gastric acid occurs in more than 75% of patients on twice-daily PPIs, and adding a histamine-2 receptor antagonist (H_2RA) at bedtime can improve nighttime acid control.[51] Whether this results in symptom relief has yet to be established. The only clinical data come from a retrospective, uncontrolled case series that reported overall symptom relief in 72% of patients.[52] Furthermore, tachyphylaxis with daily H_2RA use may blunt its effectiveness over 4 weeks.[53] The addition of an H_2RA at night is inexpensive and safe and can help some patients with nocturnal

symptoms. It may be best if an H_2RA is taken intermittently, such as before going to bed after a late or heavy meal, rather than daily.

Reflux Inhibitors

Because transient LES relaxation is the main mechanism underlying all forms of reflux, directed therapy to decrease these events appears to be the next logical step when PPIs and H_2RAs fail. However, despite aggressive pharmaceutical testing over the past 10 years, the only compound available is baclofen, a γ-aminobutyric acid type B ($GABA_B$) agonist used for many years to treat spastic muscle disorders. Baclofen decreases the number of postprandial acid and nonacid reflux events via inhibition of transient LES relaxation and reduces reflux symptoms.[54,55] The dosage of 20 mg 3 times daily has been proposed in refractory GERD. However, no controlled trials of baclofen have been conducted in PPI nonresponders, and side effects are a major issue. Baclofen crosses the blood-brain barrier, and despite progressive titration of the drug from 5 mg to 20 mg over 1 to 2 weeks, many patients experience somnolence, dizziness, and drowsiness. A number of $GABA_B$ agonists with better tolerability were developed (arbaclofen placarbil and lesogaberan), but all have been abandoned, mainly because of limited clinical efficacy.[2] I have had some success with baclofen in patients who had increased episodes of nonacid reflux (>72 per day) and related symptoms and, more recently, in 2 patients with rumination.

Pain Modulators

As already discussed, many patients with persistent symptoms despite PPI therapy have normal esophageal acid exposure and a form of visceral hypersensitivity. This appears to be the case both for patients with acid-hypersensitive esophagus and for the larger group with functional heartburn. In this situation, the use of pain modulators, such as tricyclic antidepressants, trazodone, and selective serotonin reuptake inhibitors (SSRIs), offers the best opportunity for symptom relief. They have been shown to relieve esophageal pain in patients with noncardiac chest pain,[56] but the data for refractory GERD are limited. In a recent randomized, placebo-controlled trial, the SSRI citalopram (20 mg at bedtime for 6 months) was shown to be effective in patients with acid-hypersensitive esophagus and refractory reflux symptoms.[57]

Other approaches to address visceral hypersensitivity include acupuncture and hypnotherapy. In a small series of 30 patients with refractory heartburn, acupuncture in combination with a single-dose PPI was more effective than double-dose PPIs.[58] High levels of anxiety are seen in patients with a poor correlation between symptoms and episodes of reflux.[59] In patients with noncardiac chest pain, hypnotherapy improved pain relief and decreased medication use.[60] I have used hypnotherapy in several patients with good outcome. Further studies are needed because the therapy is time-consuming and expensive.

Endoscopic Therapy

Currently, only 2 antireflux endoscopic devices are on the market: radiofrequency energy delivery at the gastroesophageal junction (Stretta, Mederi Therapeutics) and transnasal incisionless fundoplication (EsophyX, EndoGastric Solutions). The former procedure may decrease esophageal sensitivity to acid but does not decrease acid reflux.[61] Although current guidelines do not support its use in patients with GERD,[15] it may have a role as a pain modulator technique in certain patients and warrants further testing in patients with a hypersensitive esophagus or functional heartburn.[2] Small studies with transnasal incisionless fundoplication show relief of symptoms and 50% normalization of acid reflux parameters, but the long-term durability of the procedure is suspect.[62]

Antireflux Surgery

There is no doubt that laparoscopic fundoplication is a very effective therapy for controlling acid and nonacid reflux.[63] The best candidates are patients who (1) have abnormal reflux parameters while off PPIs, (2) have typical symptoms, and (3) show some response to PPIs.[28] However, some data suggest favorable outcomes in patients who have an inadequate PPI response. For example, one study reported similar 5-year postoperative outcomes in patients with abnormal acid exposure times regardless of whether their SI or SAP was positive or negative.[64] Patients with a positive SAP (acid-hypersensitive esophagus) and normal acid reflux values are also reported to do well with surgery.[65] Whether a decision for antireflux surgery can be based on abnormal nonacid reflux and symptom correlation alone is not known. The results of 2 studies[66,67] with limited follow-up have suggested that typical symptoms (heartburn and regurgitation, not extraesophageal complaints) decrease, and one of these studies[67] documented postoperative decreases in episodes of nonacid reflux. A recent medical-surgical advisory board recommends documenting abnormal acid reflux in all patients before surgery.[29] Some patients who have an acid-hypersensitive esophagus with normal reflux values may do well surgically, but their SI or SAP should be highly positive and the patients warned that the outcome is not guaranteed.[2] Currently, the added value of impedance-pH monitoring remains to be determined by prospective studies. These caveats are primarily for patients with typical reflux symptoms; all bets are off for those with primarily extraesophageal symptoms, especially those with no heartburn or regurgitation.[68,69]

Conclusions

Suspected reflux symptoms refractory to PPI therapy are common and can be a frustrating problem. Before testing, patient compliance to PPIs should be investigated, and switching PPIs or doubling the dose for 6 to 8 weeks should be considered. For nonresponders, the first diagnostic test should be upper endoscopy, but in 90% of cases, the results will be normal. Next, esophageal manometry and pH testing should be performed, usually in patients off PPIs for at least 1 week. In my experience, over 70% of these "refractory GERD" patients will be found to have normal reflux testing, and other diagnoses will need to be considered, including achalasia, gastroparesis, eosinophilic esophagitis, rumination, and aerophagia. However, more than 50% will have functional heartburn, a visceral hypersensitivity syndrome. Treating patients with PPI-refractory GERD–like symptoms can be difficult, as no medical, endoscopic, or surgical treatments have proven efficacy.

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